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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/824,036	04/14/2004	James McSwiggen	04-105-A (400.149)	6045

65778 7590 10/15/2007

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EXAMINER	
BOWMAN, AMY HUDSON	

ART UNIT	PAPER NUMBER
1635	

MAIL DATE	DELIVERY MODE
10/15/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/824,036	MCSWIGGEN, JAMES	
	Examiner	Art Unit	
	Amy H. Bowman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 July 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,13-18,20,21 and 32-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,13-18,20,21 and 32-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 April 2004 and 30 July 2007* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed 7/30/07 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 3/2/07 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

With entry of the amendment filed on 7/30/07, applicant has cancelled claims 2-12, 19 and 22-31 and added claims 32-38. Therefore, claims 1, 13-18, 20, 21, and 32-38 are pending in the application.

Applicant's arguments and/or amendments filed 7/30/07, with respect to the rejections under 35 USC 112 and 35 USC 103 have been considered and are persuasive. Therefore, the rejections have been withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of the instant claim amendments.

Response to Arguments--Priority

Applicant asserts that the present application claims priority to, *inter alia*, 60/363,124 and points to support for some of the instant claim limitations. However, application '124 does not teach a limitation wherein "between about 50 percent and

about 100 percent of the nucleotide positions of one or both strands of the siRNA molecule are chemically modified and any purine nucleotides present in the antisense strand are 2'-O-methyl purine nucleotides", as instantly recited.

Applicant asserts that the claim element reciting "about 50 to 100 percent of the nucleotides in the sense strand and about 50 to 100 percent of the nucleotides in the antisense strand are chemically modified with modifications independently selected from the group consisting of 2'-O-methyl, 2'-deoxy-2'-fluoro, 2'-deoxy, phosphorothioate and deoxyabasic modifications" is fully supported by U.S. provisional application 60/363,124. For example, pages 10-11 of that application teaches that the nucleic acid molecules can have 1-10 phosphorothioate internucleotide linkages in both strands, one or more 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro and/or universal base modified nucleotides, and a terminal cap moiety at the 3'-end, 5'-end, and/or both ends of either or both strands. The specification also teaches that the nucleic acid molecules can have 1-10 phosphorothioate internucleotide linkages in both strands, 1-10 nucleotides of the sense and/or antisense strands chemically modified with 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro and/or universal base modified nucleotides, and a terminal cap moiety at the 3'-end, 5'-end, and/or both ends of either or both strands. Based on the size of the molecule (18-27 nucleotides), Applicant submits that one skilled in the art would realize that the specification teaches that about 50-100% of the nucleotides in the antisense and sense strands are chemically modified. Furthermore, Applicant provides numerous examples of specific chemically modified nucleic acid molecules having

about 50-100% chemical modifications in that priority application, especially in Table I, pages 55-57, and Figures 3-10.

Contrary to applicant's assertion, a teaching of double stranded nucleic acid molecules with chemical modifications within the instantly recited range is not support for the specific limitation of "about 50 to 100 percent" of the nucleotides in each strand. Application '124 does not teach the specific range that is being instantly claimed and thus does not provide support for such.

Thus, the instant claims are accorded an effective filing date of 4/11/2004.

Response to Double Patenting

The claims are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3, 13-21, 30, 31 and 33-35 of copending Application No. 10/783,128.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant requests that this rejection be held in abeyance until either application is found allowable.

New Objections/Rejections

Claim Objections

Claims 33 and 35 are objected to because of the following informalities: It appears that applicant has inadvertently recited the words "and O-methyl" rather than

"are 2'-O-methyl" in claim 33. It appears that applicant has inadvertently omitted the word "a" before "pharmaceutically acceptable" in claim 35. Appropriate correction is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 13-18, 20, 21 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hayden et al. (US 2002/0187931 A1), in view of Davidson et al. (US 2004/0241854 A1), Elbashir et al. (The EMBO Journal, 2001, Vol. 20, No. 23, pages 6877-6888), Parrish et al. (Molecular Cell, Vol. 6, pages 1077-1087, 2000), Matulic-Adamic et al. (US 5,998,203), Braasch et al. (Biochemistry, 2002, Vol. 41, No. 14, pages 4503-4510), and Olie et al. (Biochimica et Biophysica Acta, 2002, 1576, pages 101-109).

Applicant's arguments that are considered relevant to the instant rejection are addressed following the instant rejection.

The invention of the above claims is drawn to a chemically modified nucleic acid molecule comprising a sense and an antisense strand, each strand is 18 to 27 nucleotides in length, the antisense strand is complementary to a human HD RNA

sequence comprising SEQ ID NO: 3582, the sense strand is complementary to the antisense strand and about 50 and about 100 percent of the nucleotides in each strand are chemically modified. The invention is further drawn to various modifications to the nucleic acid molecule, as well as to a composition comprising the nucleic acid molecule in an acceptable carrier or diluent.

Hayden et al. teach that antisense oligonucleotides can target the cellular gene or mRNA transcribed from that gene that encodes the huntingtin protein. Hayden et al. teach that the antisense oligonucleotide can be modified to exhibit desirable properties such as, for example, enhanced cellular uptake, enhanced affinity for the nucleic acid target, and increased stability in the presence of nucleases (see page 7). Hayden et al. teach that the antisense oligonucleotides comprise from about 15 to about 30 nucleotides. Hayden et al. teach compositions comprising the oligonucleotide antagonist and a pharmaceutically acceptable.

Hayden et al. do not teach siRNA duplexes specific for HD RNA, terminal caps, 3'-overhangs, terminal phosphates, or the specific modifications instantly recited.

Davidson et al. teach siRNA duplexes specific for the huntingtin gene. Davidson et al. is relied upon as further evidence that siRNA duplexes are appropriate means of inhibiting huntingtin target gene expression. Even without the Davidson et al. reference, the invention of the above claims is obvious in view of the antisense inhibition of huntingtin taught by Hayden et al.

Elbashir et al. teach siRNAs, wherein each strand is 21-23 nucleotides in length and wherein at least 19 nucleotides of the sense strand are complementary to the

antisense strand. The siRNAs taught by Elbashir et al. mediated RNAi via RISC. Elbashir et al. teach chemical modification with 2'-deoxy or 2'-O-methyl modifications. Elbashir et al. teach modification of 19% of the nucleotides of a duplex 21 nucleotides in length with 2'-deoxy modifications that retained activity, which meets the instant limitation of "about 50" percent. Elbashir et al. teach that duplexes of 21 nt siRNAs with 2 nt 3' overhangs were the most efficient triggers of RNAi (see abstract). Elbashir et al. teaches chemical modification of the 3' overhangs. Furthermore, the instant specification does not define "terminal cap" and it is not a term of the art. Therefore, the terminally modified siRNA molecules of Elbashir et al. meet the instant limitation of comprising a terminal cap. Elbashir et al. teach that a 5' terminal phosphate on the antisense strand is required for siRNA function (see page 6886, column 2).

It is noted that Elbashir et al. teaches that 100% modification of one or both strands with 2'-deoxy or 2'-O-methyl modifications abolished activity. However, none of the instantly recited claims are limited to this scope.

Matulic-Adamic et al. teach chemical modifications of double stranded nucleic acid structures. The enzymatic RNA molecules of Matulic-Adamic et al. are taught to be targeted to virtually any RNA transcript and achieve efficient cleavage (see column 1) and to be sufficiently complementary to a target sequence to allow cleavage. Matulic-Adamic et al. teach the incorporation of chemical modifications at the 5' and/or 3' ends of the nucleic acids to protect the enzymatic nucleic acids from exonuclease degradation, which improves the overall effectiveness of the nucleic acid, as well as facilitates uptake of the nucleic acid molecules (see column 2). Matulic-Adamic et al.

teach base, sugar and/or phosphate modification, as well as terminal cap moieties at the 5'-cap, 3'-cap, or both. Specifically, 3' phosphorothioates, inverted abasic moieties, and 2'-O-methyl modifications are utilized. Matulic-Adamic et al. teach 2'deoxy nucleotides and 2'-deoxy-2'-halogen nucleotides, wherein Br, CL and F are representative halogens (see column 3, for example). For example, figure 3 contains a ribozyme structure that encompasses modification of at least 20%, at least 30%, at least 40% or at least 50% of the nucleotide positions, as well as the modifications instantly claimed. The modifications can be in one or both of the strands and can be modifications of different types within the same structure.

Parrish et al. teach a chemically synthesized siRNA molecule, wherein each strand is 26 bp in length. Additionally, Parrish et al. teach a 742 nt long dsRNA with complete modification with 2'-fluorouracil modifications.

Braasch et al. teach that the need for antisense oligomers that are more potent and more selective has been widely recognized and has led to the development of chemical modifications to improve binding and selectivity (see page 4503). Braasch et al. teach goals for improving oligonucleotides including: improve pharmacokinetics, tissue distribution, and targeting; characterize the mechanism of RNA interference and its full potential for inhibition of gene expression for cell culture studies; use RNAi for in vivo inhibition of mammalian gene expression; perform comparative studies to demonstrate the relative strengths of different oligomer chemistries for given applications (i.e. morpholino versus RNAi) (see Table 2). Braasch et al. teach that if good *in vivo* uptake can be achieved, RNAi might significantly improve the ability of

oligonucleotides to have an impact (see page 4509).

Olie et al. teach that gapmer oligonucleotide chemistry, wherein three distinct regions are present, has provided antisense oligonucleotides with increased efficacy and reduced non-antisense-related toxicity and teach compositions comprising the oligonucleotides with a pharmaceutical carrier. Olie et al. added chemical modifications to ribonucleotides at either of the two ends of an oligonucleotide sequence, or the center region together with different combinations of phosphodiester/phosphorothioate backbones and investigated the effect on the activity of antisense oligonucleotides. The gapmer oligonucleotide exhibited a potent bispecific antisense activity. Olie et al. teach that gapmer chemistry is an optimal format and that these findings may have implications for the design and development of antisense oligonucleotides. Olie et al. teach that 2'-O-modifications provide additional nuclease resistance to oligonucleotides. Olie et al. teach synthesis of 20-mer chimeric antisense oligonucleotides.

It would have been obvious to synthesize a siRNA molecule targeted to human HD RNA, as Hayden et al. and Davidson et al. teach targeting human HD RNA with antisense oligonucleotides and siRNAs, respectively, wherein about 50 to 100% of the nucleotides of each strand are modified with each of the instant types of chemical modifications or combinations of chemical modifications, as well as terminal caps and 5'terminal phosphates, as each of these elements are taught by Elbashir et al., Matulic-Adamic et al., or Parrish et al.

One would have been motivated to incorporate 2'-O-methyl or 2'-deoxy modifications, as taught by Elbashir et al. and Matulic-Adamic et al., as well as a 5'-end

terminal phosphate, as taught by Elbashir et al., 2'-deoxy-2'-fluoro modifications, as taught by Parrish et al. or Matulic-Adamic et al., as well as abasic moieties and phosphorothioates, as taught by Matulic-Adamic et al., as each of these chemical modifications, as well as various combinations of chemical modifications, were known in the art to protect nucleic acids from exonuclease degradation and enhance the activity of nucleic acids, as taught by Matulic-Adamic et al. Furthermore, Elbashir et al. teach that a 5' terminal phosphate on the antisense strand is required for siRNA function (see page 6886, column 2).

The instant genus is huge, encompassing nucleic acid molecules that are modified at about 50 to 100% of the positions of each strand with a multitude of chemical modifications or a vast possibility of combinations of chemical modifications that were known in the antisense and ribozyme art. It is considered that there would be some configuration of the chemical modifications that were known in the art to benefit other nucleic acid molecules such as antisense oligonucleotides or ribozymes that would retain RNAi activity when incorporated into nucleic acid molecules. Due to the breadth of the instant claims, the teachings of Elbashir et al. are considered to be motivation with regards to extensively modifying nucleic acid duplexes to optimize the activity therein. Although Elbashir et al. teach that 100% modification of one or both strands with 2'-deoxy or 2'-O-methyl modifications abolished activity, there are no instant claims that are identical in scope to the teachings of Elbashir et al. Therefore, within the huge genus of molecules that are being instantly claimed, the teachings of

Elbashir et al. are considered to offer motivation to test various types of known chemical modifications at different percentages in order to optimize the activity of the molecule.

It is noted that ribozymes are sequence specific inhibitory nucleic acid molecules that rely on activity with a complex secondary structure. Although ribozymes are faced with the complexity of structure, it is well known in the nucleic acid art to incorporate extensive levels of chemical modification to enhance the activity of the molecule and to specifically incorporate each of the instantly recited modifications, as evidenced by Matulic-Adamic et al.

The instant specification discloses a multitude of oligonucleotide and ribozyme art regarding chemical modifications and teaches that "Such publications describe general methods and strategies to determine the location of incorporation of sugar, base and/or phosphate modifications and the like into nucleic acid molecules without modulating catalysis, and are incorporated by reference herein. In view of these teachings, similar modifications can be used as described herein to modify the siNA nucleic acid molecules of the instant invention so long as the ability of siNA to promote RNAi in cells is not significantly inhibited." (see page 100).

It is acknowledged that the specification is not to be relied upon for a source of motivation and that is not considered to be the instant case. The specification is merely being relied upon to distinguish that applicant recognized that double stranded nucleic acid modification is dependent upon the state of the art of oligonucleotides and ribozymes and that previously beneficial chemical modifications would be used with double stranded nucleic acid molecules as well.

Therefore, one would have been motivated to incorporate chemical modifications at about 50 to 100% of the nucleotide positions of each strand because Elbashir et al. teach successful inhibition of "about 50" percent of the nucleotides (8/42) and teach testing two types of chemical modifications extensively in siRNA molecules, and Parrish et al. and Matulic-Adamic et al. each teach extensive chemical modification of nucleic acids with successful inhibition of target gene expression.

Furthermore, Braasch et al. teach that the need for antisense oligomers that are more potent and more selective has been widely recognized and has led to the development of chemical modifications to improve binding and selectivity. Braasch et al. further recognize that goals to improve RNAi can be accomplished by utilizing chemical modifications. Since Braasch et al. teach that chemical modifications yield more potent and more selective antisense oligomers, such as oligomers for RNAi, and Elbashir et al., Matulic-Adamic et al., and Parrish et al. teach modified double stranded nucleic acid molecules that inhibit target gene expression, the gene expression of Elbashir et al. and Parrish et al. being inhibited by RNAi, one would have been motivated to synthesize duplexes with different levels of modifications to optimize the activity of the molecule.

Additionally, antisense oligonucleotides, ribozymes, and dsRNAs are each commonly used for sequence-specific mRNA knockdown and each of these encounters the same problems for effective application. Therefore, one would have been motivated to utilize the same modifications and techniques that have been utilized to overcome these problems with antisense oligonucleotides or ribozymes with siRNAs to add the

same benefits to RNAi technology.

For example, Olie et al. teach that gapmer oligonucleotide chemistry, wherein three distinct regions are present, has provided antisense oligonucleotides with increased efficacy and reduced non-antisense-related toxicity. Olie et al. teach that combinations of different modifications at different regions of the oligonucleotide have been tested in order to optimize oligonucleotide activity. Olie et al. teach stepwise experimentation of modifications throughout oligonucleotides in order to find the optimal configuration. Olie et al. is relied upon as evidence that it is common to experiment with different known modifications at different locations to optimize oligonucleotide activity and to deliver nucleic acids in a composition with a carrier.

Therefore, one would have been motivated to apply such a method to incorporate known modifications at various locations and amounts, as taught by Olie et al., into the antisense oligonucleotides of Hayden et al. or to utilize another known inhibitory molecule, such as the siRNA duplexes that were synthesized by Davidson et al.

Finally, one would have a reasonable expectation of success given that each of the modifications were known in the art at the time the invention was made to add benefits to antisense oligonucleotides, ribozymes or siRNA duplexes, as evidenced by Hayden et al., Elbashir et al. (EMBO), Matulic-Adamic et al., Parrish et al. and Olie et al., wherein each of the molecules face the same challenges, and each of which can be improved with modifications, as evidenced by Braasch et al. Since Olie et al. teach effectively walking modifications across antisense oligonucleotides to optimize the

combination of modifications as well as the location of the modifications and Elbashir et al. and Parrish et al. teach successfully synthesizing modified double stranded nucleic acid molecules, one would reasonably expect for modifications at various percentages to benefit the double stranded nucleic acid molecules targeted to HD RNA, as evidenced by Davidson et al. Furthermore, the instant target sequence had been previously targeted and inhibited with antisense oligonucleotides and siRNA duplexes, as evidenced by Hayden et al. and Davidson et al., respectively.

Since Elbashir et al., Matulic-Adamic et al., and Parrish et al. teach extensive modification of double stranded nucleic acid molecules and Olie et al. teach experimentally determining optimal locations and levels of modification of antisense oligonucleotides, incorporating the modifications at various percentages in the double stranded nucleic acid molecules of Elbashir et al. is considered within the realm of routine optimization.

It is noted that Elbashir et al. teach that 100% modification of one or both strands with 2'-deoxy or 2'-O-methyl modifications abolished activity. However, regardless of the results of these specific modifications at 100% of the positions of one or both strands, Elbashir et al. did modify duplexes and published data regarding successful inhibition with some duplexes and unsuccessful inhibition with others, supporting that testing of such known chemical modifications is routine in the art. The results of Elbashir et al. are considered to offer motivation to incorporate chemical modifications at various percentages to optimize the activity of the duplex because not all modifications result in activity at every percentage.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Response to Applicant's arguments that are considered pertinent to the instant rejection under 35 USC 103(a)

Applicant argues that Hayden teach single stranded antisense molecules targeted to the HD gene rather than molecules with separate sense and antisense strands and that Davidson does not teach chemical modifications in the siRNAs targeted to HD RNA. Applicant argues that Matulic-Adamic teach chemical modification of ribozymes and Olie et al. teach chemical modification of antisense oligonucleotides and asserts that this is non-analogous art.

It is noted that this is not a rejection under 35 USC 102, but rather 35 USC 103 and therefore each individual reference does not need to teach every element of the instant claims to render the claims obvious in view of the combination of references. Applicant's arguments directed to each of the references not teaching each of the elements of the instant claims are not considered persuasive. Furthermore, applicant asserts that Davidson is not art because the instant claims should be accorded an effective filing date of 3/11/02. Contrary to applicant's assertion, as explained in the "Response to Priority" section above, the instant claims are accorded an effective filing date of 4/11/04.

Single-stranded antisense oligomers, ribozymes, and siRNA molecules have

each been chemically modified with the same or similar chemical modifications to enhance delivery of each of the molecules, each of which are sequence specific inhibitors of target gene expression that rely on the activity of an antisense strand. Although each of the molecules functions via a different mechanism, this is irrelevant to the fact that it was known in the art at the time of filing that each of these types of inhibitory molecules benefit from chemical modifications.

Furthermore, although applicant asserts that these technologies are non-analogous art, the instant specification discloses a multitude of oligonucleotide and ribozyme art regarding chemical modifications and teaches that "Such publications describe general methods and strategies to determine the location of incorporation of sugar, base and/or phosphate modifications and the like into nucleic acid molecules without modulating catalysis, and are incorporated by reference herein. In view of these teachings, similar modifications can be used as described herein to modify the siNA nucleic acid molecules of the instant invention so long as the ability of siNA to promote RNAi in cells is not significantly inhibited." (see page 100).

It is acknowledged that the specification is not to be relied upon for a source of motivation and that is not considered to be the instant case. The specification is merely being relied upon to distinguish that applicant recognized that double stranded nucleic acid modification is dependent upon the state of the art of oligonucleotides and ribozymes and that previously beneficial chemical modifications would be used with double stranded nucleic acid molecules as well.

Applicant asserts that Tuschl expressly teaches away from highly modified

siRNA constructs because Tuschl teaches that extensive substitution with 2'-deoxy or 2'-O-methyl modifications abolishes RNAi activity. Applicant concludes that Tuschl thus expressly states that more than a few end modifications should be avoided. Applicant's interpretation of the Tuschl reference is considered erroneous. It is noted that Tuschl et al. teach that 100% modification of one or both strands with 2'-deoxy or 2'-O-methyl modifications abolished activity. This is the only teaching regarding abolished activity and importantly, there are no instant claims that are commensurate in scope with this teaching of Tuschl et al. However, regardless of the results of these specific modifications at 100% of the positions of one or both strands, Tuschl et al. did modify duplexes and published data regarding successful inhibition with some duplexes and unsuccessful inhibition with others, supporting that testing of such known chemical modifications is routine in the art. The results of Tuschl et al. are considered to offer motivation to incorporate chemical modifications at various percentages to optimize the activity of the duplex because not all modifications result in activity at every percentage. Tuschl et al. is silent as to chemical modification at percentages other than the 19% (8/42 nucleotides) modification that worked and the 100% modification with 2'-deoxy or 2'-O-methyl modifications that abolished activity. Additionally, the 19% modification of Tuschl et al. meets the instant limitation of "about 50%".

Parrish et al. teach siRNA molecules and teach incorporation of 2'-deoxy-2'-fluoro modifications into long dsRNA, wherein the extensive chemical modification resulted in RNA interference activity. Similar to Tuschl et al., Parrish et al. supports that testing of known chemical modifications is routine in the art and is considered to offer

motivation to incorporate chemical modifications at various percentages to optimize the activity of the duplex because not all modifications result in activity at every percentage.

Applicant asserts that none of the references, alone or in combination render obvious the presently claimed nucleic acids because the cited references do not teach or suggest all of the claimed elements. Applicant has not pointed to any specific element of the claims that are not taught by the combination of references cited by the examiner. The cited references teach molecules with the same structural characteristics that are instantly recited that are targeted to the same target sequence, as evidenced by Davidson; and teach the instant chemical modifications, as evidenced by Tuschl, Parrish, Matulic-Adamic, Olie and Hayden.

Applicant concludes that the references do not render obvious the instantly claimed methods of synthesizing chemically modified nucleic acid molecules, although the instant claims are not directed to methods, but are rather directed to compounds.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In *re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 13-18, 20, 21 and 32-38 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 11-25 of copending Application No. 11/450,856. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims are each directed to chemically modified double stranded nucleic acid molecules targeted to human HD RNA, wherein the molecules each have the same types of chemical modifications and structural characteristics. The instant claims and the claims of application '856 are considered obvious variants of each other.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy H. Bowman whose telephone number is (571) 272-0755. The examiner can normally be reached on Monday-Thursday 6:30 - 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Doug Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Amy H. Bowman

Examiner
Art Unit 1635

AHB

/J. E. Angell/
Primary Examiner
Art Unit 1635